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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,481	12/18/2001	Miquel Sales Amill	INL-048	3281

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EXAMINER	
DAVIS, DEBORAH A	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/022,481	SALES AMILL ET AL.	
	Examiner	Art Unit	
	Deborah A Davis	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *23-31 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response to the Notice of Informal Amendment mailed on July 2, 2004 has been acknowledged. Currently, claims 1-22 and 32 are under consideration for examination. Claims 23-31 and 33 are withdrawn. Claims 1, 3, 14-18 has been amended.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-4, 7, and 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kenji et al (EP 0 476 545) in view of Noguchi et al (USP#4,843,021).

Kenji et al teaches the instant claims by disclosing a method for an immunoassay comprising a first particle (fine particle A) bound to the second member (Anti-IgE) and reacting the them with a sample (serum) to form a first complex (column 7, lines 15-31) with an unbound first member (IgE antigen) present in the sample (column 7, line 20). A second particle (fine particle B) bound to a third member (IgE monoclonal antibody), that is different from the second member because both anti-IgE antibodies recognize different binding sites (column 6, lines 30-40) and being capable of binding to the first member (column 7, lines 15-30). One of the two antibodies is bound together with a fluorescent substance to a fine particle (A) and the other antibody is bound together with a quencher to a fine particle (B) (column 3, lines 36-50). The second particle (fine particle B) bound to the third member (Anti-IgE antibody) is reacted with the sample (IgE antigen) to form a second complex such that two kinds of anti-IgE monoclonal antibodies recognizing different sites forms a sandwich assay (column 4, lines 45-48). The assay was measured at a wavelength of 495nm (column 7, lines 21-23). Kenji et al discloses various incubation times that were carried out in different examples in the range of 0.5 – 40 minutes, that would satisfy step (b) of claim 1 (column 9, lines 49-58). Although the Kenji et al reference does not specifically recite a composition, the components of the composition as recited in claim 18 are taught by the instant reference such that it teaches a first particle (fine particle A) bound to the second member (anti-IgE) and a second particle (fine particle B) bound to a third member (IgE monoclonal antibody) with both antibodies being different wherein they recognize

different binding sites, therefore it is the examiner's position that the Kenji et al reference satisfies the instant claim and all that depend therefrom.

Kenji et al differ from the instant claim in not teaching measuring turbidity.

However, Noguchi et al teaches an immunological assay method wherein the concentration of a substance to be assayed can be determined in several ways, one being and increase or decrease in light scatter which is caused by a change in the turbidity accompanying the formation of an antigen-antibody complex reaction (column 2, lines 1-54). Several instruments can be used for determination of the turbidity or a change therein caused by antigen/antibody complex reaction, such as turbidimeter, spectrophotometer or photometer (column 5, lines 37-56).

It would have been obvious to one of ordinary skill in the art to modify the teachings of Kenji et al to include the measurement of antibody-antigen reaction in a sample as taught by Noguchi et al to detect changes in a sample and be able to calculate the concentration based on the turbidity changes in a sample.

5. Claims 5-6, 8-9, 18-22 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kenji et al (EP 0 476 545) in view of Noguchi et al (USP#4,843,021) and in further view of Koike et al (USP#5,187,067).

The teachings of Kenji in view of Noguchi are set forth above and differ from the instant claims in not teaching protein S and C4b-binding protein.

However, Koike et al teaches immunological determination of free human protein S (1st member) and C4BP (2nd member) -protein S complex in a sandwich format

utilizing monoclonal antibodies affixed to insoluble latex carriers (abstract). This method of detection permit measurement of free human protein S or C4bp-protein S complex in an assay sample (i.e. plasma) with good accuracy without variations in the quality of reagents. Protein S and C4bp-protein S complex can be measured directly, and accurate measurement within short periods of time. The determination methods of this invention permit diagnosis of the conditions of thrombosis having cancer as a basic disease, nephrosis and accurate determination of fibrinolytic state of toxemia of pregnancy (column 3, lines 1-35). Plasma samples were taken from normal healthy subject as well who did not exhibit disease and patients who did (column 15, lines 1-12). Protein S and C4BP-protein S complexes were compared and measured (column 15, lines 15-55). These assays can be formed in a two-step method (sequentially) comprising contacting the sample with the fixed primary antibody and then a second antibody or by a one-step method the secondary antibody simultaneously with the primary antibody (column 4, lines 32-68).

It would have been obvious to one of ordinary skill in the art to modify the assays of Kenji et al in view of Noguchi to include the detection and measurement of protein S and its C4b-binding protein as taught by Koike et al because it offers great advantages to medicine wherein determination of these proteins can permit diagnosis of conditions related to cancer and toxemia in pregnant patients. One would be motivated to detect such proteins to determine early diagnoses and treatment.

6. Claims 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kenji et al in view of Noguchi et al as applied to claim 1 and further in view of Mischak et al (USP#6,124,430).

The teachings of Kenji et al in view of Noguchi et al are set forth above and differ in the instant claims in not teaching molar ratios.

However, Mischak et al teaches immunoassays to quantify protein levels in plasma, serum and whole blood. The assay can be carried out either in a sandwich or competition format (column 7, lines 20-45). In a sandwich type assay, the antibody is normally employed in amounts substantially in molar excess of the maximum amount of protein expected to be in the sample (column 8, lines 1-10). Preferably, the antibodies chosen to carry out the sandwich type assay are selected such that the first antibody, which is brought into contact with the protein in the sample, does not bind all or part of the epitope recognized by the second antibody, thereby significantly interfering with the ability of the second antibody to bind the protein.

It would have been obvious to one of ordinary skill in the art to modify the teachings of Kenji et al in view of Noguchi to include molar ratios taught by Mischak et al because it is known in the art that when sandwich assays are utilized, different antibodies in molar access such as monoclonal and polyclonal are selected so that both antibodies recognizing the same epitopes with a range in close proximity will not overlap (column 7, lines 20-52). It has long been held to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "Where the general conditions of a claim are disclosed in the

prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454, 456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. At 458, 105 USPQ at 236-237. The "discover of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Voesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980).

Response to Arguments

7. Applicant argument that the reference of Kenji et al does not disclose determining turbidity or agglutination as recited in newly amended claim one is found to be persuasive and the 102 rejection is hereby withdrawn. However, a new 103 rejection to address the new limitation has been set forth above.

8. Applicant argument that the reference of Kenji et al does not disclose protein S and C4BP in the newly amended claims 18 is found to be persuasive, however, a new 103 rejection to address the new limitation has been set forth above.

9. Applicant argument that the reference of Koike et al does not disclose or suggest turbidity or agglutination assays is noted but not found to be persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections

are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The reference of Noguchi et al teaches measuring concentration of a reaction based on turbidity changes in a sample, which is addressed in the 103 rejection above.

10. Applicant's argument that the rejection under 103 that includes claim 9 is improper because Koike et al does not disclose a second member that is a C4BP, this argument is noted but not found persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The second member of the assay has been established in the reference of Kenji et al and the teaching of Koike et al teaches motivation to detection particular proteins such as C4BP and S-protein. Examiner directs applicant to the modified rejection above.

11. Applicant argument that Koike et al do not disclose all of the elements in the composition is noted but not found to be persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208

USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the reference of Kenji et al in view of Koike et al teaches the combined composition that includes the teaching of protein S and C4BP.

12. Applicant's argument that the reference of Noguchi et al does not disclose detecting turbidity or agglutination generated by the binding of two members to an antigen at different epitopes is noted but not found persuasive.

In response to applicant's argument, the reference of Noguchi et al is relied on for its teaching of taking measurements of a reaction with turbidity readings which also provides a motivation for its use.

13. Applicant's argument that the reference of Mischak and does not teach turbidity or agglutination and there would not be motivation to combine this reference with Kenji is noted but not found to be persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the reference of Mischak and Kenji both teach sandwich assay formats in detection of complexes. But,

the teaching of Mischak was relied on upon for its teaching of molar ratios. The reference of Mischak teaches that different antibodies in molar access such as monoclonal and polyclonal are selected to that both antibodies recognizing the same epitopes with a range in close proximity will not overlap (column 7, lines 20-52), this method is performed to control the reaction of the instant reagents involved in an assay. Further, the use of reagents in certain concentrations are viewed as optimization.

Conclusion

14. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah A Davis whose telephone number is (571) 272-0818. The examiner can normally be reached on 8-5 Monday thru Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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